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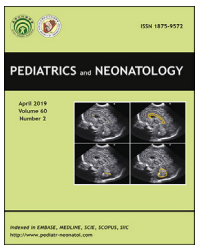

Original Article

Diagnostic values of C-reactive protein and complete blood cell to identify invasive bacterial infection in young febrile infants

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Key Words
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Abstract *Background:* Newborn infants younger than 3 months old with a fever are frequently evaluated for the risk of invasive bacterial infections (IBIs), which include bacteremia and/or bacterial meningitis, in the pediatric emergency department (PED). The purpose of this study was to determine the individual complete blood cell count and biochemistry levels associated with IBIs in febrile infants.
Methods: We carried out this retrospective study using a pediatric emergency department at a tertiary medical center in southern Taiwan, where we also evaluated the clinical characteristics and routine blood tests between experimental groups.
Results: We enrolled 1231 febrile infants under the age of 3 months old in this study. We found higher body temperature, neutrophil percentage, and C-Reactive protein (CRP) values and a lower hemoglobin level in the IBIs group. Furthermore, a CRP value greater than 25 mg/L can predict IBIs at a better rate than the group with values lower than 25 mg/L (11.7% vs. 2.1%, Odds ratio 6.3, $p < 0.001$).
Conclusion: This study provides evidence that a CRP level greater than 25 mg/L can more accurately predict IBIs in febrile infants. Furthermore, lower hemoglobin levels were also found in IBIs. Nevertheless, additional laboratory tests are needed to identify young febrile infants with IBIs.

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1. Introduction

Young infants under the age of 3 months with fever are frequently evaluated for the risk of invasive bacterial infections (IBIs), which consists of bacteremia and/or bacterial meningitis, in the pediatric emergency department (PED).[1,2] However, reliable physical examination findings and routinely individual laboratory investigations are not currently available to help clinicians differentiate benign viral infections or a case of over-swaddling from serious bacterial infections in febrile infants. In such patients, urinary tract infections are the most common bacterial infections,[3] and the use of urinalysis is a highly noninvasive and sensitive test that can help clinicians in the PED to diagnose it.[4] However, differentiating low-risk IBIs in young febrile infants without a tailored source or unnecessary antibiotic exposure poses quite a challenge for clinicians.[5]

Earlier this year, a large cohort study of prospectively enrolled young febrile infants uncovered that using complete blood cell count parameters or optimal thresholds does not have high accuracy in identifying febrile infants with IBIs.[6] The risk of bacteremia is higher in infants under one year old than in other age groups. Previous studies have discussed elevated C-reactive protein (CRP) levels in children with bacteremia and monitoring CRP level as an indicator of sepsis.[7,8] While substantial evidence has increased with regard to the laboratory evaluation of young febrile infants with IBIs, CRP[9,10] and procalcitonin[9,11] can more accurately predict which young infants have IBIs, with procalcitonin actually performing better than CRP in identifying patients with IBIs.[12,13] Specific ribonucleic acid biosignatures[14] and inflammatory cytokines[15] have recently been discovered in febrile patients with IBIs. However, these new biomarkers are not readily available in all PED and still require further validation.

The purpose of this study was to determine the vital signs and routinely individual laboratory investigations in infant febrile patients with IBIs. We further identified optimal thresholds using receiver operating characteristic curves for IBIs.

2. Materials and methods

2.1. Study design

This study is a retrospective, cohort study conducted at the PED of Kaohsiung Chang Gung Medical Hospital in southern Taiwan between Jan. 1, 2007 and Dec. 31, 2013. The institutional review board of the Chang Gung Medical Foundation approved this study. All the records and information of both patients and physicians were anonymized and de-identified prior to analysis. All patients aged 0–3 months old who visited the PED with the clinical symptom of infection or fever were included in the study, and IBIs were defined as bacteremia or bacterial meningitis.[6] All patients' vital signs at triage and laboratory tests were recorded. The primary outcome of this study was to describe the potential for IBIs in young febrile infants based on their clinical parameters.

2.2. Data analysis

All data are presented as the mean. We analyzed quantitative data using Student's t-test and adopted the Chi-square test in calculating the different frequencies between groups. Binary regression was performed for selected data, and we used receiver operating characteristic curve analysis for determining individual contributing factors and cut-off values for specific risk factors. The statistical analysis was carried out using IBM SPSS Statistics for Windows (version 22).

3. Results

During this seven-year period, 239,459 visits were made to our PED, and 1231 patients were less than 3 months old and were thus enrolled in the study. Patients' demographics, clinical parameters, and PED disposition are provided in Table 1. Body temperature was significantly higher in the IBIs group (38.2 °C vs. 37.8 °C, $p = 0.022$) in the PED triage. The parameters of age, gender, heart rate, and blood pressure did not differ between groups. Laboratory studies were also described, in which both the neutrophil percentage (48.6% vs. 41.6%, $p = 0.004$) and CRP level (62.5 mg/L vs. 18.4 mg/L, $p < 0.001$) were significantly higher in the IBIs group. Furthermore, hemoglobin levels were lower in the IBI group (10.9 g/dL vs 11.5 g/dL, $p = 0.038$), while white blood cell (WBC) count, creatinine, aspartate aminotransferase, and blood sugar levels demonstrated no significant differences (Table 1). Prolonged hospital stays (15.4 days vs. 6.8 days, $p < 0.001$) were also found in the IBIs group (Table 1). Clinical outcomes related to IBI showed no significant differences in discharge, admission rate, or antibiotics usage in the PED (Table 1). Significant differences were still observed between the IBIs and non-IBIs groups with regard to body temperature, neutrophil percentage, hemoglobin, and CRP (mg/L) after adjusting for age and gender. The area under the curve of these factors is shown in Table 2. CRP was ultimately chosen as the determining factor because of its acceptable discrimination, and the best cut-off value was calculated at 25 mg/L. CRP levels greater than 25 mg/L better predict the IBIs rate than values under 25 mg/L (11.7% vs. 2.1%, $p < 0.001$). The odds ratio for predicting invasive bacterial infection based on CRP level >25 mg/L was 6.3 (confidence interval: 3.35–11.68).

4. Discussion

Deciding outpatient management of a fever in febrile infants without focus poses quite a challenge for clinicians. Mintegi et al. concluded that certain young febrile infants at low risk (which includes good appearance, older than 21 days of age, no pyuria, absolute neutrophil count ≤10 000, CRP ≤20 mg/L, procalcitonin <0.5 ng/mL, and no clinical changes during a 24-h-stay at the PED) can be managed as outpatients without antibiotics.[16] Our analysis includes 1231 febrile infants under 3 months old. We observed higher body temperatures during triage in the PED, neutrophil percentage, and CRP values and a lower

Table 1 Characteristics of young infants (<3 months old) in the pediatric emergency department (PED).

	Controls	Invasive bacterial infections			p-value
Numbers	1182	49			
		Bacteremia	Bacterial Meningitis	Both	
		28	26	5	
Mean Age (days)	46.8	45.4			0.722
Gender					
Male N (%)	734 (62.1%)	32 (65.3%)			0.764
Disposition					
Discharge	59	0			0.166
Admission	1087	48			
Transferred to other hospitals	46	1			
Length of hospital stay (days)	6.8	15.4			**<0.001**
Antibiotics use in PED N (%)	477 (40.4%)	25 (51.0%)			0.141
Body temperature (°C)	37.8	38.2			**0.022**
Pulse rate (/min)	153	169			0.145
Systolic blood pressure (mmHg)	91	90			0.819
White blood cells (1000/uL)	11.5	12.2			0.449
Neutrophil percentage (%)	41.6	48.6			**0.004**
Hemoglobin (g/dL)	11.5	10.9			**0.038**
CRP (mg/L)	18.4	62.5			**<0.001**
Sugar (mg/dL)	94.1	98.9			0.467
Creatinine (mg/dL)	0.3	0.3			0.702
AST (IU)	40.2	57.2			0.336

All data are presented as the mean of group.
p values <0.05 are presented as bold type.

Table 2 Significant parameters after adjusting for age and gender.

Parameters	Controls	Invasive bacterial infections			p-value
		aOR	95% confidence interval	Area under the curve	
Body temperature (°C)	1	1.564	1.171–2.088	0.605	0.002
Neutrophil percentage (%)	1	1.027	1.008–1.046	0.583	0.005
Hemoglobin (g/dl)	1	0.823	0.693–0.976	0.560	0.026
CRP (mg/L)	1	1.017	1.012–1.022	0.743	<0.001

aOR: adjusted odds ratio.

hemoglobin level in the IBIs group. Of greater importance, our findings demonstrate that CRP values greater than 25 mg/L have a higher discriminatory ability in identifying which young febrile infants have IBIs.

Body temperature and heart rate also appear to be elevated, and diastolic pressure instead of systolic blood pressure appears lower in the bacteremia group, which is in line with the previous consensus describing the pattern of septicemia in children.[17] However, vital signs in the PED can vary greatly and may not serve as useful indicators for obtaining blood cultures when dealing with individuals.

In line with previous prospective results in young infants for IBI,[6] we found that WBC count has a poor ability to differentiate between young febrile infants with and without IBIs in PEDs. Due to the low incidence of IBIs, most abnormal WBC results are not associated with the presence of an IBI. Since a procalcitonin assay is much more expensive than CRP and is not readily available in all PEDs, we determined the best cut-off level of CRP for better diagnostic accuracy. Our data revealed that CRP values greater than 25 mg/dl has better diagnostic accuracy for predicting IBS.

In this study, we observed lower hemoglobin levels in the IBIs group, even when adjusting for patient age. As we already know, inflammation-related anemia represents a highly prevalent and important clinical problem.[18] Ballin et al. demonstrated that bacteremia is accompanied by a significant decrease in hemoglobin levels in children lacking evidence of hemolytic anemia[9] while iron levels are strong disease outcome predictors in intensive care unit patients.[19] Hepcidin is a key regulator of iron homeostasis, just as a thermal controller is for room temperature.[20,21] Inflammation-induced hepcidin interacts with ferroportin, which becomes internalized and degraded and ultimately leads to intracellular iron sequestration and decreased iron absorption in the duodeum.[22] Furthermore, hepcidin-induced low iron levels were related to both the long-term and short-term survival rates of critically ill individuals.[19,23] In addition to iron homeostasis, hepcidin has an important antimicrobial effect, especially against

Escherichia coli,[24] which is the most common pathogen in young febrile infants.[25]

In conclusion, we demonstrated in this study that CRP levels greater than 25 mg/L can predict IBIs in febrile infants with greater accuracy. Furthermore, lower hemoglobin levels were found in the IBIs group. However, better laboratory tests are required to identify IBIs in young febrile infants.

Conflicts of interest

The authors hereby declare to have no conflicts of interest related to this article.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.pedneo.2018.06.004.